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Original Article

Prognostic values of CEA, CA19-9, and CA72-4 in patients with stages I-III colorectal cancer

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Abstract: Objective: The purpose of this study was to explore the relationship between the levels of three tumor markers (TMs), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and CA72-4, and the prognoses of colorectal cancer patients. Methods: From January 2012 to December 2015, 101 patients with stages I-III colorectal cancer treated in the general surgery department of Nanfang Hospital, Southern Medical University were included in this retrospective study. The patients' blood was collected at different time points to determine their biochemical index values. The CA19-9 and CEA levels were measured using a chemiluminescence analyzer, and the CA72-4 level was determined using a semi-automatic enzyme-free analyzer. The relationship between the tumor marker expressions and the prognoses of patients with colorectal cancer was analyzed. Results: The sensitivity of the combined quantification of the three TMs was higher than quantifying just one of them, but the specificity was decreased. Those three TM levels were stable at two years after the operations, and they were significantly lower than they were before the operations ($P < 0.05$). A Kaplan Meier survival curve analysis showed that, compared with the patients with normal levels, the patients with increased levels of the three TMs had significantly shorter overall survival times and higher recurrence rates ($P < 0.05$). Conclusion: The combined quantification of CEA, CA19-9, and CA72-4 is of great significance in determining the prognoses of colorectal cancer patients. It is helpful to predict the outcomes of patients with stages I-III colorectal cancer two years after their operations.

Keywords: CEA, CA19-9, CA72-4, prognosis, colorectal cancer

Introduction

Colorectal cancer is one of the most common malignant tumors in humans, and its incidence rates rank third and second among men and women worldwide, respectively [1]. With the changes in living habits, diet, and the atmospheric environment, the incidence of colorectal cancer in China is increasing, and it is now ranked fifth and fourth in the mortality rates of males and females with malignant tumors [2]. However, the onset of colorectal cancer is insidious, and most patients already have advanced cancer at the time of their diagnosis. Therefore, effective tumor markers (TM) that can help find early colorectal cancer lesions are important because they can enable earlier treatment and will have a significant effect on reducing the mortality of patients with colorectal cancer.

Serum TMs are a type of substance synthesized directly by tumor cells and released into the blood or released by the body in the process of responding to tumor cells. The detection of serum TMs is convenient, fast, non-invasive, and easy to accept for patients, and the TMs are of great significance in helping diagnose the disease, providing treatment guidance, monitoring for metastasis or recurrence, and judging prognosis [3-6]. Therefore, the selection of appropriate tumor markers helps improve the diagnosis and prognosis of tumors. The purpose of this study is to evaluate the prognostic value of CEA, CA19-9, and CA72-4 in patients with stages I-III colorectal cancer.

Materials and methods

Subjects

From January 2012 to December 2015, 101 patients with stages I-III colorectal cancer who were treated in the general surgery department of Nanfang Hospital, Southern Medical Univer-

sity were recruited for this retrospective study. Inclusion criteria: (1) patients with colorectal cancer or rectal cancer diagnosed through histopathology; (2) patients with a complete resection of the primary tumor; (3) patients in stages I-III as determined by the tumor-node-metastasis (TNM) stages established by the American Joint Committee on Cancer (AJCC); (4) patients without distant metastasis; (5) patients who signed the informed consent form; (6) patients with complete pathological results and postoperative follow-up data. Exclusion criteria: (1) patients who could not be confirmed as having colorectal cancer or rectal cancer through histopathology; (2) patients with an unknown pathological stage or patients in stage IV; (3) patients who received preoperative treatment (radiotherapy, chemotherapy, etc.); (4) patients who died of non-tumor causes; (5) patients also suffering from other cancers; (6) patients who refused to sign the informed consent form. This study was approved by the Ethics committee of Nanfang Hospital, Southern Medical University. All the patients signed informed consent before participating in this study.

Measurement of the serum CEA, CA19-9, and CA72-4

The patients with colorectal cancer were followed up for 24 months. The CEA, CA19-9, and CA72-4 levels were measured before the operations and at 1 month, 3 months, 6 months, 12 months, and 24 months after operations. A total of 4 ml of fasting venous blood was collected and centrifuged within 1 h. The CA19-9 and CEA levels were measured using an ACS-A80 chemiluminescence analyzer (Bayer, Germany), and the CA72-4 level was determined using a semi-automatic enzyme immunoassay (Deling, USA).

Positive criteria

CEA: the normal range is 0-5 ng/ml, and the positive range is > 5 ng/ml. CA19-9: the normal range is 0-35 U/ml, and the positive range is > 35 U/ml. CA72-4: the normal range is 0-6.9 U/ml, and the positive range is > 6.9 U/ml.

Statistical analysis

The statistical analysis was done using SPSS 20.0 (International Business Machines, Corp., Armonk, NY, USA). All the data were expressed as the means ± standard deviation (SD). The measurement data were analyzed using t-tests, and the count data were analyzed using χ^2 tests. The Kaplan-Meier method was used for the survival analysis. The differences were considered statistically significant when $P < 0.05$.

Results

Comparison of the clinical characteristics among the positive and negative groups and the three serum TM levels

There were statistically significant differences in terms of age, gender, depth of invasion, TNM stage, lymph node metastasis, recurrence within two years after the operation, and the Dukes stage between the CEA positive group and the CEA negative group ($P < 0.05$). However, there were no significant differences in terms of hypertension, diabetes, tumor location, tumor size, pathological type, or tumor differentiation between the CEA positive group and the CEA negative group ($P > 0.05$). In addition, there were significant differences in tumor location, TNM stage, lymph node metastasis, recurrence within two years after the operation, and Dukes stage between the Serum CA19-9 positive group and the negative group ($P < 0.05$). However, there were no significant differences in terms of age, gender, hypertension, diabetes, tumor size, pathological type, tumor differentiation degree, or infiltration depth between the serum CA19-9 positive group and the negative group ($P > 0.05$). Moreover, there were significant differences in hypertension, TNM stage, lymph node metastasis, recurrence within two years after the operation, and Dukes stage between the serum CA72-4 positive group, and the negative group ($P < 0.05$). However, there were no significant differences in terms of age, gender, diabetes, tumor location, tumor size, pathological type, tumor differentiation degree, or infiltration depth between the serum CA72-4 positive group and the negative group ($P > 0.05$). The clinical characteristics are shown in **Table 1**.

Evaluation of the diagnostic value of the three TMs individually and jointly

As shown in **Table 2**, the sensitivity, specificity, positive predictive value, and negative predictive value of CEA, CA19-9, and CA72-4 in the diagnosis of colorectal cancer were calculated

Table 1. Relationship between the serum CEA, CA199, and CA724 levels and the clinical characteristics of patients with colorectal cancer

Variables	N	CEA		*P*	CA19-9		*P*	CA72-4		*P*
		≤ 5	> 5		≤ 35	> 35		≤ 6.9	> 6.9	
Ages				0.009*			0.533			0.190
< 50	38	11	27		15	23		16	22	
≥ 50	63	35	28		21	42		35	28	
Gender				0.013*			0.552			0.170
Male	71	38	33		24	47		39	32	
Female	30	8	22		12	18		12	18	
Hypertension				0.520			0.247‡			0.041*
No	88	39	49		29	59		41	47	
Yes	13	7	6		7	6		10	3	
Diabetes				0.197			1.000‡			0.118
No	90	43	47		32	58		43	47	
Yes	11	3	8		4	7		8	3	
Tumor location				0.839			0.035*			0.362
Colon	56	25	31		25	31		26	30	
Rectum	45	21	24		11	34		25	20	
Tumor size				0.785			0.292			0.768
≤ 4	49	23	26		20	29		24	25	
> 4	52	23	29		16	36		27	25	
Pathological type				0.995			1.000‡			0.723
Adenocarcinoma	90	41	49		32	58		46	44	
Mucous	11	5	6		4	7		5	6	
Degree of tumor differentiation				0.741			0.561			0.429
Poorly differentiated	15	7	8		4	11		6	9	
Moderately differentiated	63	27	36		22	41		31	32	
Highly differentiated	23	12	11		10	13		14	9	
Depth of invasion				0.017*,†			0.345†			0.362†
T1/T2	5	5	0		3	2		4	1	
T3/T4	96	41	55		33	63		47	49	
TNM stage				0.009*			0.001*			0.035*
I/II	45	27	18		24	21		28	17	
III	56	19	37		12	44		23	33	
Lymph node metastasis				0.001*			0.003*			0.004*
No	47	30	17		24	23		31	16	
Yes	54	16	38		12	42		20	34	
Recurrence within two years after operation				0.032*			0.001*			0.001*
Yes	68	36	32		32	36		42	26	
No	33	10	23		4	29		9	24	
Dukes stages				0.003*			0.002*			0.033*
Stage A	3	3	0		3	0		2	1	
Stage B	42	26	16		21	21		28	14	
Stage C	56	17	39		12	44		21	35	

Note: *$P < 0.05$; †Fisher's exact test; ‡continuous correction chi square.

based on the upper limit of the reference range. The results showed that the sensitivity of each TM single measurement was lower, but the sensitivity of the combined measurement was sig-

Table 2. I Comparison of three TMs in colorectal cancer patients

Measurement indexes	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
CEA	54.5	98.4	98.2	57.0
CA19-9	64.4	96.8	97	62.5
CA72-4	49.5	95.2	94.3	53.6
Combined measurement	88.1	91.9	94.7	82.6

Table 3. The levels of three TMs in patients with colorectal cancer before and after their operations

Variables	Preoperative	Preoperative	Preoperative	Preoperative	Preoperative
CEA	7.13 ± 6.57	4.06 ± 3.64*	4.52 ± 3.96*	5.47 ± 4.03*	7.16 ± 6.12
CA19-9	44.45 ± 31.88	17.68 ± 10.78*	16.10 ± 10.41*	19.30 ± 22.05*	20.16 ± 17.83*
CA72-4	9.95 ± 7.17	3.92 ± 1.97*	5.62 ± 2.85*	6.18 ± 3.94*	7.80 ± 6.01*

*$P < 0.05$ vs. preoperative.

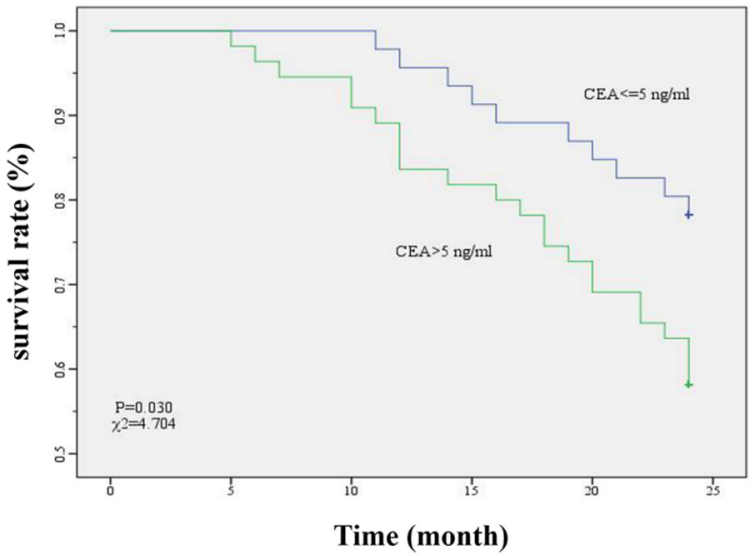

Figure 1. A Kaplan-Meier survival curve analysis of the relationship between the serum CEA levels and the postoperative survival times of patients with colorectal cancer.

nificantly higher than the sensitivity of the single measurement, but its specificity was decreased.

Comparison of the CEA, CA19-9, and CA72-4 levels before and after the operations

The levels of the three TMs were higher before the operations, and they were significantly decreased after the operations. There was a significant difference between the TM levels after the operations and the levels before the operations ($P < 0.05$) (**Table 3**). In addition, as the postoperative time increased, the TM levels tended to increase.

The relationship between the three TM levels and postoperative survival and prognosis

In the two years of follow-up, there were 33 patients with postoperative recurrences. The TMs of the patients who did not have a recurrence in the two years after their operations were always at low levels, but in the 33 patients who had a recurrence, the tumor markers increased significantly. The results of the Kaplan-Meier survival curve and the log-rank tests showed that the tumor marker levels in the CEA positive group, the CA19-9 positive group, and the CA72-4 positive group were significantly correlated with the early recurrence of colorectal cancer ($P < 0.05$) (**Figures 1-3**). A further analysis of the relapsed patients showed that in the 33 patients with recurrences, the recurrence probability was 6% (2/33), 27% (9/33), 24% (8/33), and 43% (14/33) during the periods 1-6, 6-12, 12-18, and 18-24 months after the operations, respectively. The probability of recurrence was highest at 12-24 months after the operations, a period that included 67% (22/33) of the patients. It showed that the risk of recurrence was high in patients with stages I-III colorectal cancer during the period 12-24 months after the operation, and it was mainly concentrated during the period

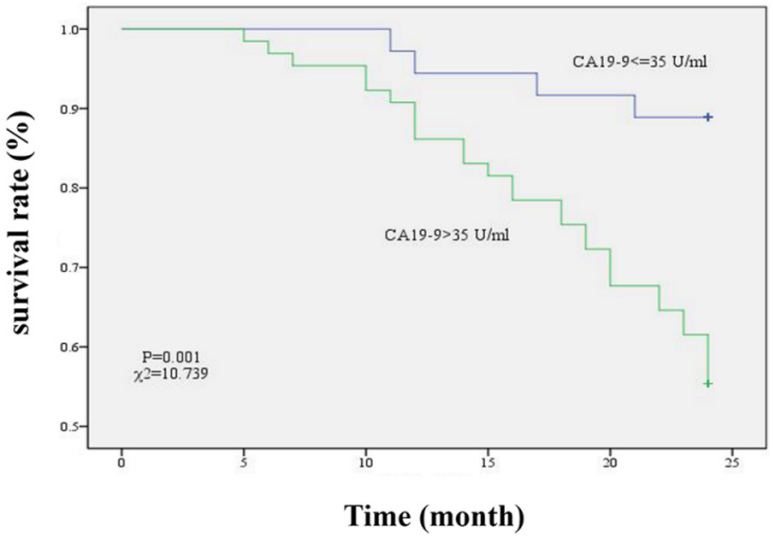

Figure 2. A Kaplan-Meier survival curve analysis of the relationship the between serum CA19-9 levels and the postoperative survival times of patients with colorectal cancer.

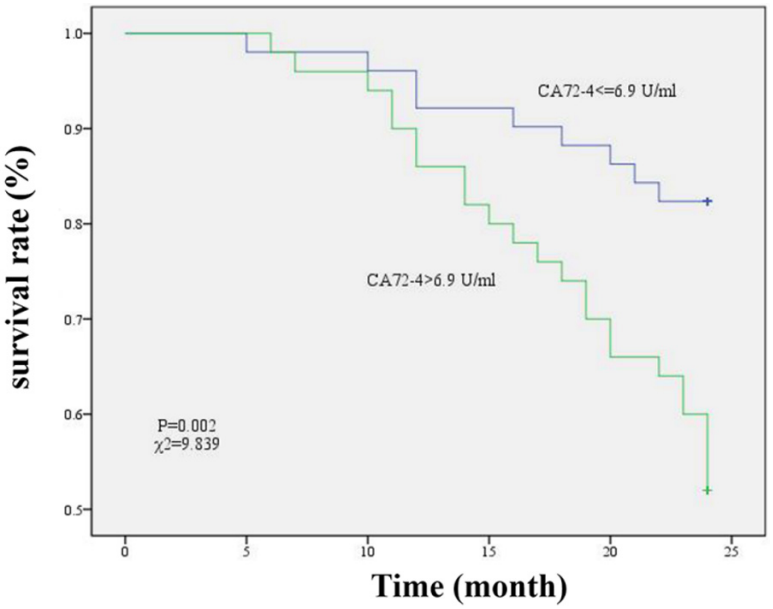

Figure 3. A Kaplan-Meier survival curve analysis of the relationship between the serum CA72-4 levels and the postoperative survival times of patients with colorectal cancer.

18-24 months after the operations, accounting for 43% (14/33) of the patients with recurrences after the operations (**Figure 4**).

Discussion

Colorectal cancer is one of the most common malignant tumors worldwide and has a high incidence. Due to its hidden onset and low early diagnosis rate, it is mostly advanced at the time of diagnosis and seriously threatens human health. The specificity of fecal occult blood is poor, and colonoscopy operations, CT, and PET-CT are complex and expensive, so it is difficult to increase colorectal cancer screenings in physical examinations and in outpatients. In recent years, the measurement of TMs is often used as an auxiliary examination to diagnose colon cancer. It is easy to do, reasonable in cost, and high in patient compliance, but the sensitivity and specificity of a single TM are poor. Now, the combined measurement of two or more TMs is often used to improve the sensitivity and specificity, and it can provide an early diagnosis and effectively evaluate patients' prognoses. Many tumor markers in the serum have been shown to be valuable in the diagnosis and prognostic evaluation of patients with colorectal cancer, such as CEA, CA19-9, CA72-4, MMP, and TIMP [7].

At present, CEA, CA19-9, and CA72-4 are the most commonly used colorectal cancer tumor markers at home and abroad. In China, more than two combined tests are used, and simultaneous studies have been conducted on patients with stages I-IV colorectal cancer [7, 8]. However, most of the foreign countries adopt a single or two joint test, but there has been no research on the joint analysis of the three TMs [9, 10]. In this study, we only discussed the relationship between the preoperative and postoperative TM levels and the prognoses in the patients with stages I-III colorectal cancer. Our results showed that the higher the three TMs levels, the higher the TNM stage, the deeper the depth of the tumor invasion, the

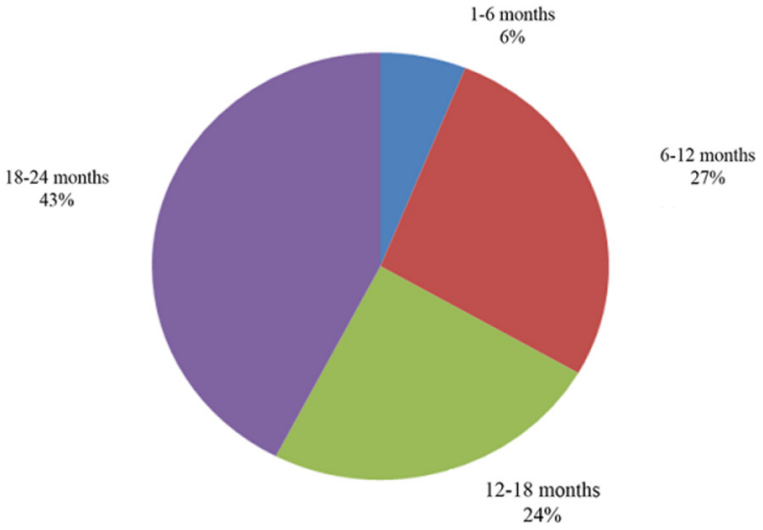

Figure 4. The distribution of the 33 patients who had recurrences during the two-year follow-up period.

greater the possibility of lymph node metastasis before the operation, and the greater the probability of recurrence at two years after the operation, suggesting that the three TMs levels are helpful in predicting the patients' conditions and have a certain value in predicting the recurrence of colorectal cancer. Secondly, the results of this study also show that the sensitivity of a single index is relatively low. The sensitivities of CEA, CA19-9, and CA72-4 are 54.5%, 64.4%, and 49.5%, respectively. The sensitivity of the combined measurement of CEA, CA19-9, and CA72-4 is significantly improved, reaching 88.1%. This shows that the parallel combined detection is of great value in the diagnosis of colorectal cancer, which is similar to the findings of other studies [4, 7, 8]. This method is suitable for screening healthy physical examinees or outpatients without specific gastrointestinal symptoms. Combined with a targeted colonoscopy, it can improve the detection rate of early colorectal cancer.

TM can be used to evaluate the curative effect of colorectal cancer, monitor the recurrence, and judge the prognosis, especially with advanced tumors [8, 9]. The results of this study show that the serum TM levels in the patients after their operations were decreased to different degrees. The patients returned to the hospital for reexamination at 1, 3, 6, 12, and 24 months after their operations, and the three TM levels were measured each time. We found that the decreases in the TMs after the operations were statistically significant in comparison with their levels before the operations, an indication that the tumor marker levels can be reduced by surgical resection of the tumors, so the operation can be said to effectively improve the survival rate of colorectal cancer patients. Colonoscopy, B-ultrasound, CT, MRI, PET-CT, and other comprehensive examinations were used to determine whether the tumors recurred. 33 patients had a recurrence within 2 years of their final diagnoses. The recurrence rate was 33%. Two patients died as a result of their recurrences, so the mortality rate was 2%. The recurrence and mortality rates are lower than the rates reported in previous studies, and the patients' survival times are longer than the times reported in previous studies [11].

Some studies have shown that 82.4% of patients have a re-elevation of the TMs 1-3 months before recurrence or metastasis, and the higher the TM level, the worse the prognosis [12-14]. In this study, 90.9% of the patients with recurrences had higher TM levels 1-4 months before, and more significantly during the 12-24 months before, which is consistent with the results of the previous study [9]. The results indicate that the combined measurement of CEA, CA19-9, and CA72-4 can predict the postoperative recurrence of colorectal cancer.

We also found that the average age of the 33 patients with recurrences was 51.8 years old, and the patients included 23 males and 10 females. The recurrence rates at 1-6, 6-12, 12-18, and 18-24 months after the operations were 6% (2/33), 27% (9/33), 24% (8/33), and 43% (14/33), respectively. It can be seen that the recurrence rate at 12-24 months after the operations was the highest, reaching 67% (22/33), indicating that the recurrence risk of stages I-III colorectal cancer patients is high at 12-24 months after the operations, and is mainly concentrated at 18-24 months after the operations, accounting for 43% (14/33) of the recurrence patients.

In conclusion, the combined measurement of CEA, CA19-9, and CA724 in this study was of great significance in determining the prognosis of colorectal cancer. The combined measurement will help predict the prognosis of patients with stages I-III colorectal cancer two years after surgery.

Disclosure of conflict of interest

None.

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